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Coronary artery disease in lung transplant candidates: role of routine invasive assessment

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Abstract: **BACKGROUND:** An atherosclerotic disease burden sufficient to put lung transplant candidates at risk for end-organ disease after transplantation is considered to be a relative contraindication for lung transplantation. **OBJECTIVES:** The aim of this study was to assess our current practice of cardiac workup by coronary angiography in lung transplant candidates 50 years of age. **METHODS:** We retrospectively analyzed 50 consecutive lung transplant candidates 50 years of age in which coronary angiography was performed at the University Hospital Zurich (2009-2013). For every patient, the risk of developing an acute coronary event was estimated by using a recalibrated version of the PROCAM study calculator for the Swiss population. **RESULTS:** The median estimated risk of developing an acute coronary event within 10 years in the study cohort ($n = 50$) was 4.2% (interquartile range 1.9-7.6), which is considered to be a low risk. Sixteen percent of patients were considered to be at intermediate risk. In 66% of patients, coronary angiography showed no coronary artery disease (CAD). In 28% of patients, CAD without significant stenosis was diagnosed. In 6% of patients, significant coronary stenosis was detected requiring percutaneous coronary intervention. No correlation between the coronary status and the risk score or cardiovascular risk profile was found. **CONCLUSIONS:** The high prevalence of asymptomatic CAD in lung transplant candidates without correlation to a common clinical risk score supports the important role of coronary angiography for the assessment of coronary artery status. This approach might prevent cardiovascular events and improve long-term survival after transplantation.

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Coronary Artery Disease in Lung Transplant Candidates: Role of Routine Invasive Assessment

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Key Words

Coronary artery disease · Lung transplant candidates ·
Routine invasive assessment · Coronary angiography

Abstract

Background: An atherosclerotic disease burden sufficient to put lung transplant candidates at risk for end-organ disease after transplantation is considered to be a relative contraindication for lung transplantation. **Objectives:** The aim of this study was to assess our current practice of cardiac workup by coronary angiography in lung transplant candidates ≥ 50 years of age. **Methods:** We retrospectively analyzed 50 consecutive lung transplant candidates ≥ 50 years of age in which coronary angiography was performed at the University Hospital Zurich (2009–2013). For every patient, the risk of developing an acute coronary event was estimated by using a recalibrated version of the PROCAM study calculator for the Swiss population. **Results:** The median estimated risk of developing an acute coronary event within 10 years in the study cohort ($n = 50$) was 4.2% (interquartile range 1.9–7.6), which is considered to be a low risk. Sixteen percent of patients were considered to be at intermediate risk. In 66% of patients, coronary angiography showed no coronary artery disease (CAD). In 28% of patients, CAD without significant stenosis was diagnosed. In 6% of patients, significant coronary stenosis was detected requiring percutaneous coronary

intervention. No correlation between the coronary status and the risk score or cardiovascular risk profile was found.

Conclusions: The high prevalence of asymptomatic CAD in lung transplant candidates without correlation to a common clinical risk score supports the important role of coronary angiography for the assessment of coronary artery status. This approach might prevent cardiovascular events and improve long-term survival after transplantation.

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Introduction

The recently published adult lung and heart-lung transplant report of the International Society for Heart and Lung Transplantation (ISHLT) emphasizes that the age distribution of lung transplant recipients has shifted to the elderly: since 1985, the median age of recipients has gradually increased; almost 66% of lung transplant recipients are now aged 45–65 years [1]. The treatment with calcineurin inhibitors, which is a class of immunosuppressive drugs commonly used in all lung transplant recipients, aggravates the cardiovascular risk profile by in-

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creasing the incidence of hypertension, diabetes mellitus, and dyslipidemia [2]. In order to prevent cardiovascular events (especially myocardial infarction), a careful evaluation of the coronary arterial status of elderly transplant candidates becomes even more important, since age is a well-known additional cardiovascular risk factor. Moreover, the prevalence of cardiovascular risk factors increases with age.

An atherosclerotic disease burden sufficient to put the lung transplant candidate at risk for end-organ disease after transplantation is considered to be a relative contraindication for lung transplantation [3]. The assessment of cardiovascular status, especially the presence of coronary artery disease (CAD), therefore is an important part of the pre-transplant workup. This is also stated in a consensus document for the selection of lung transplant candidates by the ISHLT [3], although the definitive clinical evidence of the prognostic impact is still lacking [4, 5].

Coronary angiography can detect abnormal morphology of coronary arteries that can be treated and, at least in part, may affect long-term outcome following lung transplantation [2]. To date, the cardiovascular assessment at our Lung Transplant Program at the University Hospital Zurich includes medical history, electrocardiography, echocardiography, and, in lung transplant candidates over the age of 50 years, routine coronary angiography. The aim of this study was to assess our current practice of cardiac workup among lung transplant candidates and possibly update this practice if shortcomings are detected.

Methods

We audited the current clinical practice at our institution evaluating lung transplant candidates aged >50 years for CAD by coronary angiography. The coronary arterial status was routinely assessed by a coronary angiography and classified into 3 categories. First, if no coronary plaques could be detected, the coronary status was defined as normal. Second, in the presence of wall irregularities (coronary sclerosis) or plaques of $\leq 50\%$ stenosis, CAD without significant stenosis was diagnosed. Third, the presence of one or more stenoses of $> 50\%$ was defined as significant CAD. According to guidelines [6, 7], functional assessment of the severity of coronary stenosis by fractional flow reserve was not routinely performed.

We retrospectively analyzed 50 consecutive patients aged 50 years or older in which coronary angiography was performed during assessment for lung transplantation at the University Hospital Zurich in the years 2009–2013.

For every patient, the risk of developing an acute coronary event was estimated by using a recalibrated version of the PROCAM study calculator for the Swiss population, known in

Table 1. Baseline characteristics of the included patients

Sex	
Male	32 (64)
Female	18 (36)
Age, years	59 (54.5–62)
Diagnosis	
COPD	27 (54)
IPF/UIP	13 (26)
Others	10 (20)
Cardiovascular risk factors	
Smoking history	38 (76)
Hypertension	20 (40)
Dyslipidemia	6 (12)
Adiposity	11 (22)
Diabetes	6 (12)
Family history of CAD	7 (14)
AGLA risk calculator, %	4.2 (1.9–7.6)

Values are n (%) or median (interquartile range). IPF = Idiopathic pulmonary fibrosis; UIP = usual interstitial pneumonia.

Switzerland as the ‘AGLA risk calculator’ [8, 9]. We hypothesized that a correlation between the estimated risk of cardiovascular events and the coronary arterial status could be found, and consequently, the indication for performing coronary angiography in lung transplantation candidates may be optimized. All data are shown as medians and interquartile ranges (IQR).

The local research ethics committee granted approval for this study (Ethics Committee of the Canton of Zurich; KEK-ZH No. 2013-0460).

Results

The study group consisted of 50 consecutive patients, aged 50 years or older, in which coronary angiography was performed during assessment for lung transplantation at the University Hospital Zurich in the years 2009–2013.

In the study cohort ($n = 50$), the median age was 59.0 years (IQR 54.5–62.0), and 32 patients (64%) were male. The most frequent diagnosis leading to lung transplantation in the study group was chronic obstructive pulmonary disease (COPD; 54%) followed by pulmonary fibrosis (idiopathic pulmonary fibrosis and usual interstitial pneumonia; 26%). A smoking history and arterial hypertension were the most prevalent cardiovascular risk factors (76 and 40%, respectively). Baseline characteristics of patients are shown in table 1.

The median estimated risk of developing an acute coronary event within 10 years was 4.2% (IQR 1.9–7.6), which is considered to be a low risk according to the cur-

rent Swiss guidelines (www.agla.ch). Just 8 patients (16%) had a score of $\geq 10\%$, which is considered to be an intermediate risk.

In about two thirds of patients (66%), coronary angiography showed no CAD. However, in 28% of patients, CAD without significant stenosis was diagnosed. In 3 patients (6%), significant coronary stenosis was detected requiring percutaneous coronary intervention with stenting. Figure 1 shows the findings of coronary angiography.

Only 3 of 8 patients (37%) with a risk score $\geq 10\%$ had pathological coronary angiography, and 14 of 17 patients (82%) with pathological coronary angiography were classified as low risk for coronary events using the AGLA risk calculator.

The prevalence of cardiovascular risk factors in the subgroup with normal coronary angiography compared to those with CAD did not differ significantly.

In the subgroup with normal coronary angiography, the median risk according to the AGLA risk calculator was 4.2% (IQR 2.2–7.7), whereas in the subgroup with pathological findings in the coronary angiography, the median risk was 4.4% (IQR 1.5–6.7). Table 2 summarizes the findings of the two subgroups.

Discussion

A clinical audit is a systematic review of procedures intended to improve quality and outcome of patient care [10]. This audit carried out at our institution aimed to evaluate the current practice in the assessment of coronary status of lung transplant candidates aged 50 years or older. An analysis of the obtained data revealed several interesting results.

Firstly, asymptomatic CAD was present in almost a third of lung transplant candidates aged 50 years or older, which represents a high prevalence. This finding confirms data from previously published series [11, 12]. Of interest, the median risk estimated by the AGLA calculator was low with just a few patients identified as having an intermediate and high risk for coronary events.

Secondly, the AGLA risk score was not correlated with coronary status. The median score in the group with normal coronaries was almost identical to the score of those patients with coronary pathologies as assessed by the gold standard method, coronary angiography. With the exception of dyslipidemia for which the low number of patients precludes further conclusions, no significant differences in the presence of cardiovascular risk factors were found between the two groups. In addition, only a minor-

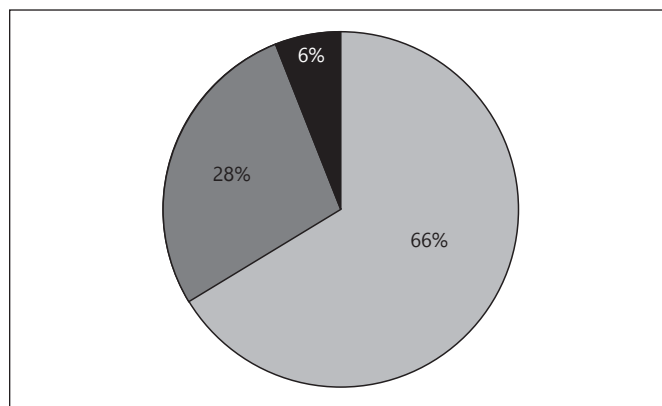


Fig. 1. Coronary angiography in lung transplant candidates. Percentage of patients with normal coronary arteries (light grey), with nonsignificant CAD (dark grey), and significant CAD (black).

Table 2. Characteristics of patients with normal coronaries and coronary artery disease

	Normal (n = 33)	Pathological (n = 17)
Sex		
Male	18 (55)	14 (82)
Female	15 (45)	3 (18)
Age, years	59 (54–60)	60 (57–62)
Diagnosis		
COPD	17 (52)	10 (59)
IPF/UIP	7 (21)	6 (35)
Others	9 (27)	1 (6)
Cardiovascular risk factors		
Smoking history	24 (73)	14 (82)
Hypertension	14 (42)	6 (35)
Dyslipidemia	2 (6)	4 (24)
Adipositas	8 (24)	3 (18)
Diabetes	5 (15)	1 (6)
Family history of CAD	5 (15)	2 (12)
AGLA risk calculator, %	4.2 (2.2–7.7)	4.4 (1.5–6.7)

Values are n (%) or median (interquartile range). IPF = Idiopathic pulmonary fibrosis; UIP = usual interstitial pneumonia.

ity of patients considered to be at least at intermediate risk showed pathologies of the coronary vessels, and most of the patients with coronary atherosclerosis were classified as low risk as assessed by the risk score using parameters available before the invasive assessment with coronary angiography.

The power of these results may be limited by the fact that the epidemiological PROCAM risk calculator was

developed to predict the 10-year risk of myocardial infarction in the general population. However, several studies [13, 14] suggested that epidemiological risk scores might correlate with subclinical atherosclerosis and, as such, might be used as a surrogate marker of coronary anatomy.

Thirdly, the main pulmonary diagnosis for which patients were referred for lung transplant assessment seems not to be associated with an increased prevalence of CAD. This is an unexpected finding since the diagnosis of COPD itself is considered to portend additional cardiovascular risk due to the common risk factor of smoking [15, 16]. The findings from our study might be biased by the fact that the included patients did not have typical cardiovascular symptoms prior to referral, while symptomatic patients probably underwent assessment for coronary disease elsewhere before routine assessment for lung transplantation at our institution. Conversely, in our study, CAD was more frequently found in patients with a diagnosis of pulmonary fibrosis. One might assume that systemic inflammatory mechanisms also involve the coronary vessels as previously reported [17]. However, the small sample size of our retrospective study is not adequately powered for a definitive conclusion.

Our results have several implications. The commonly used recalibrated PROCAM risk calculator does not seem to be able to predict coronary artery risk in the highly selected population of lung transplant candidates. In our cohort, the risk score showed low positive (0.40) and negative (0.66) predictive values. Designed as a clinical audit, our study was not adequately powered to quantify the predictive performance of the PROCAM risk calculator. However, these data confirm that an epidemiological

score, which was validated for the general population, cannot be directly translated to selected patient subgroups and its routine use in this setting cannot be recommended.

In order to prevent cardiovascular events (e.g. myocardial infarction) and improve long-term survival after lung transplantation, the assessment of coronary artery status before transplantation is an important part of the pre-transplant workup. In the presence of coronary atherosclerosis, patients undergoing lung transplantation are considered to be at an increased risk for end-organ disease and, therefore, risk factors should be treated aggressively.

Considering these facts, especially the relatively high prevalence of asymptomatic CAD in lung transplantation candidates and the lack of correlation with a common clinical risk score, a careful evaluation of coronary status by angiography seems to be a reasonable approach in our view.

The high diagnostic power that is achieved, the possibility of treating significant stenosis and performing advanced hemodynamic measurements by a single procedure, and the low risk profile at high-volume centers [18] offer significant advantages of the invasive technique as compared to noninvasive methods (CT, SPECT, PET, and MRI).

In addition, our data suggest that in light of these advantages, cardiac evaluation by coronary angiography should probably be extended even to patients below the age of 50 years when assessed for lung transplantation. Where an age cutoff should be set for the performance of a coronary angiography in this specific population with end-stage pulmonary disease would be a matter of investigation in a larger future study.

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